• Review Article •

Neurodegeneration as an early driver and therapeutic target in diabetic retinopathy

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Abstract

● Diabetic retinopathy (DR) is conventionally recognized as a microvascular complication of diabetes mellitus. Nevertheless, accumulating evidence confirms that early retinal neurodegeneration develops in the course of diabetes and drives early visual impairment. Multiple studies have verified that abnormal retinal neural responses frequently emerge before identifiable microvascular lesions. This review therefore systematically summarizes existing evidence confirming retinal neurodegeneration as a core, early pathological event in diabetic retinal disease (DRD), elaborates the cellular and metabolic mechanisms of neurodegeneration inside the retinal neurovascular unit (NVU), and assesses novel neuroprotective therapeutic modalities. Retinal neurodegeneration manifests prior to clinically apparent microvascular complications. NVU dysfunction, triggered by neuroinflammation, oxidative stress, advanced glycation end products (AGEs), excitotoxicity and mitochondrial dysfunction, serves as the pivotal pathway mediating neuronal injury. Notably, current vasculotropic therapies fail to effectively block early neuronal dysfunction. By comparison, neuroprotective interventions targeting oxidative stress, inflammatory cascades, glial dysfunction, deficient neurotrophic supply and mitochondrial damage exhibit promising effects on maintaining retinal neuronal architecture and function. In conclusion, retinal neurodegeneration constitutes a core pathological cascade of DR. Incorporating neuroprotective regimens into established treatment systems facilitates earlier intervention, optimizes visual function prognosis, and ultimately transforms the clinical management paradigm of DRD toward retinal neural protection.

● **KEYWORDS:** diabetic retinopathy; retinal neurodegeneration; neurovascular unit; diabetic retinal disease; neuroinflammation

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INTRODUCTION

Diabetic retinopathy (DR) is one of the most common and severe complications of diabetes mellitus and remains a leading cause of preventable vision loss among working-age adults worldwide. Traditionally, DR has been classified and managed as a microangiopathy, with disease staging and therapeutic decision-making largely based on visible retinal vascular abnormalities, including microaneurysms, capillary occlusion, vascular leakage, and pathological neovascularization[1-2]. This vascular-centric paradigm has dominated clinical practice for decades and has guided the development of current treatments such as laser photocoagulation and anti-vascular endothelial growth factor (VEGF) therapy. However, increasing clinical and experimental evidence indicates that this classical view does not fully explain the complex pathology of diabetic retinal disease (DRD)[3]. DRD is defined as a multifaceted disorder incorporating both neurodegenerative and microvascular components within the diabetic retina.

Functional visual deficits, including delayed implicit times on multifocal electroretinography (mfERG), reduced contrast sensitivity, and impaired dark adaptation, have been detected in diabetic patients before the appearance of clinically detectable microvascular lesions[4-5]. Notably, mfERG abnormalities often arise in retinal regions that subsequently develop microvascular lesions, suggesting that early neural dysfunction may precede and predict later vascular pathology. In parallel, structural

alterations such as thinning of the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) have been observed using optical coherence tomography (OCT) in patients without overt DR, suggesting early neuronal involvement[6-7]. Although functional and structural abnormalities do not always spatially overlap, their frequent coexistence in early diabetes indicates coordinated impairment of neural signaling and cellular integrity rather than isolated defects[6-7]. Together, these functional and structural changes point toward a shared underlying disturbance in retinal homeostasis.

Among the vision-threatening manifestations of DR, diabetic macular edema (DME) represents the principal cause of visual impairment. Importantly, DME can occur at any stage of the disease, from non-proliferative DR to proliferative DR, and is not confined to advanced vascular pathology[2,8-9]. This clinical observation challenges the notion that retinal vascular damage alone accounts for visual loss in DR and highlights the contribution of nonvascular mechanisms, including neural and glial dysfunction, to disease progression[4]. Over the past two decades, a growing body of literature has demonstrated that diabetes induces early and progressive neurodegenerative changes in the retina. Retinal neurodegeneration, characterized by neuronal apoptosis, synaptic dysfunction, and glial activation, has been identified as an early and, in some cases, independent pathological event in DR[5,7]. Several comprehensive reviews have further proposed that diabetic retinal neurodegeneration may precede and actively contribute to subsequent microvascular pathology, rather than simply arising as a downstream consequence of vascular damage[4,10].

These findings have prompted a conceptual transition from viewing DR as a purely vascular disease toward recognizing it as a disorder of the retinal neurovascular unit (NVU)[11]. The NVU comprises retinal neurons, Müller cells, astrocytes, microglia, endothelial cells, and pericytes, which together maintain retinal metabolic homeostasis, blood-retinal barrier (BRB) integrity, and neurovascular coupling[10]. Within this integrated framework, functional deficits detected by mfERG and structural changes revealed by OCT can be interpreted as complementary manifestations of NVU dysregulation affecting neuronal signaling, glial support, and vascular responsiveness[11]. Damage to any component of this integrated unit can disrupt retinal function and structural stability. Accordingly, the term DRD has been proposed to more accurately reflect the combined neurodegenerative and microvascular pathology observed in diabetes[8,10,12]. Experimental and clinical studies suggest that dysfunction of neuronal and glial components of the NVU contributes to BRB breakdown, inflammatory amplification, and subsequent microvascular abnormalities, supporting a model in which neural and vascular pathologies are mechanistically interdependent rather than hierarchically vascular-dominant[13-14].

In this context, the present review aims to provide a comprehensive synthesis of current clinical and experimental evidence supporting retinal neurodegeneration as an early and central pathological component of DRD. By integrating functional abnormalities detected by mfERG with structural alterations revealed by optical coherence tomography, this review places neural and glial dysfunction within the broader framework of NVU dysregulation and its contribution to visual impairment. Furthermore, emerging neuroprotective and NVU–stabilizing therapeutic strategies are discussed, with particular attention to their translational relevance and the challenges that currently limit clinical implementation. Despite substantial advances in vascular-targeted therapies, current treatments primarily address late-stage microvascular complications and do not adequately prevent or reverse early neuronal injury[15-16]. By clearly defining these objectives and structure, this review aims to provide a coherent framework for understanding DR as a neurovascular degenerative disease and to inform future diagnostic and therapeutic strategies.

To ensure a comprehensive synthesis of the available evidence, a systematic literature search was conducted using PubMed, Embase, and Web of Science databases in January 2026. We prioritized literature published within the last five years, and also include the pioneering works from the past ten years. The selection criteria focused on peer-reviewed articles, including randomized clinical trials, observational studies, and biologically plausible preclinical models, to provide a comprehensive overview.

RETINAL NEURODEGENERATION PRECEDES MICROVASCULAR DAMAGE IN DIABETIC RETINOPATHY

Retinal Neurovascular Unit The concept of the NVU provides a structural and functional framework for understanding how neural and vascular pathologies are interlinked in DR[11]. The NVU is composed of retinal neurons, Müller cells, astrocytes, microglia, endothelial cells, and pericytes, which together regulate retinal metabolism, synaptic activity, BRB integrity, and neurovascular coupling[12]. Under physiological conditions, these cellular components operate as a tightly coordinated unit, ensuring adequate nutrient delivery, waste removal, and maintenance of retinal homeostasis.

In diabetes, chronic hyperglycemia disrupts this finely balanced system. Rather than affecting retinal blood vessels in isolation, metabolic stress simultaneously impairs neuronal signaling, glial support functions, and vascular stability[13]. As emphasized in recent reviews, NVU dysfunction represents an early and fundamental pathological event in DRD, preceding clinically detectable microangiopathy[10]. This integrated view

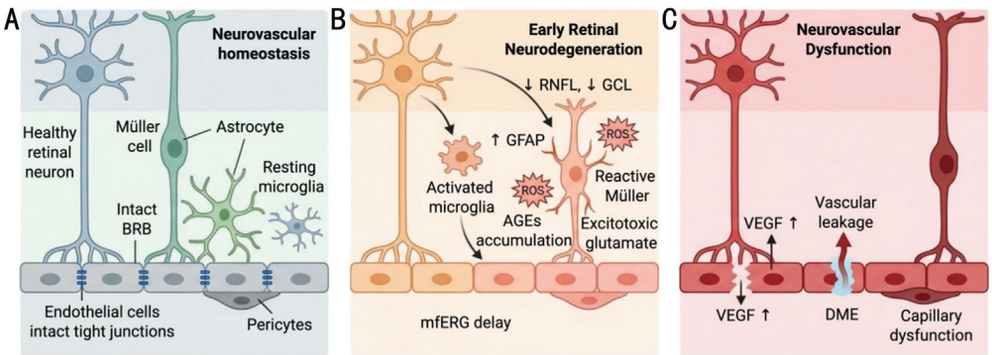

Figure 1 Neurodegeneration-centered model of diabetic retinopathy This schematic illustrates the progression of diabetic retinopathy from retinal neurovascular homeostasis to neurodegeneration-driven microvascular pathology. A: Under physiological conditions, retinal neurons, Müller cells, astrocytes, microglia, endothelial cells, and pericytes form an intact NVU, maintaining neuronal function, vascular stability, and BRB integrity. B: In early diabetes, neuronal dysfunction and structural changes occur prior to clinically detectable vascular lesions, including delayed mfERG responses and thinning of the RNFL and GCL, GFAP upregulation. These changes are accompanied by glial activation, metabolic stress, and impaired neurovascular coupling, highlighting early neurodegeneration as a key initiating event. C: With disease progression, sustained NVU disruption promotes VEGF upregulation, blood-retinal barrier breakdown, vascular leakage, DME, and capillary dysfunction, ultimately driving overt microvascular pathology. BRB: Blood–retinal barrier; GFAP: Glial fibrillary acidic protein; NVU: Neurovascular unit; mfERG: Multifocal electroretinography; RNFL: Retinal nerve fiber layer; GCL: Ganglion cell layer; VEGF: Vascular endothelial growth factor; DME: Diabetic macular edema; AGEs: Advanced glycation end products.

challenges the traditional compartmentalization of neural and vascular pathology and highlights the NVU as a central target for understanding disease initiation.

This review emphasizes the centrality of neurodegeneration in DR. However, neural and vascular pathologies are fundamentally interdependent. While neurodegeneration often precedes microvascular changes, vascular-related complications remain the primary cause of severe visual impairment as the disease progresses to advanced stages. In proliferative DR, neovascularization and fibrovascular proliferation are the primary causes of catastrophic vision loss (*e.g.*, vitreous hemorrhage, tractional retinal detachment)[17]. Furthermore, DME is primarily a consequence of BRB breakdown and changes in vascular permeability[18]. Therefore, emphasizing neurodegeneration does not negate the importance of vascular mechanisms; rather, it provides a more holistic view of DRD as a coupled neurovascular disorder, where early neural interventions might prevent these late-stage vascular complications.

Evidence of Early Neural Dysfunction and Structural Loss Prior to Vascular Lesions Compelling evidence indicates that retinal neurodegeneration occurs early in diabetes, often before the appearance of ophthalmoscopically visible vascular abnormalities[3]. Functional studies using mfERG have consistently demonstrated delayed implicit times and localized neuronal dysfunction in diabetic patients without clinically apparent DR[3-4]. Notably, these functional delays have been shown to predict the future development of microvascular lesions in corresponding retinal regions, suggesting that neural dysfunction may serve as an early indicator of subsequent vascular pathology[5].

Structural imaging studies further support the presence of early neurodegeneration. OCT has revealed thinning of the RNFL and GCL in diabetic individuals without clinical signs of retinopathy, indicating loss of retinal ganglion cells and axonal integrity at a preclinical stage[6-7]. These findings have been reproduced across different patient cohorts and imaging platforms, reinforcing the notion that neuronal loss is not merely a late consequence of ischemic vascular damage. Importantly, these early functional and structural neural changes cannot be fully explained by subclinical microvascular abnormalities alone. As discussed by previous studies, the temporal dissociation between neurodegeneration and overt microangiopathy argues against a purely vascular-driven model of disease initiation and instead supports a paradigm in which neural impairment arises as an early and partially independent pathological process[1,5]. As illustrated in Figure 1, DR is characterized by early neuronal dysfunction and glial activation within the retinal NVU, which precede clinically detectable microvascular lesions and contribute to subsequent blood-retinal barrier breakdown and vascular pathology.

CELL-TYPE SPECIFIC NEUROINFLAMMATORY MECHANISMS IN DIABETIC RETINAL NEURODEGENERATION

Neuroinflammation is a hallmark of early diabetic retinal neurodegeneration and represents a central mechanism linking metabolic stress to neuronal dysfunction within the retinal NVU. Rather than reflecting a uniform inflammatory response,

diabetic retinal inflammation is highly cell type-specific, involving distinct but interconnected roles of microglia, Müller cells, and astrocytes. These glial populations respond differentially to hyperglycemia-induced stress and collectively shape the neurodegenerative microenvironment that precedes overt microvascular pathology[19-20].

Microglia Microglia are the resident immune cells of the retina and serve as the first responders to metabolic and oxidative stress in diabetes. In the diabetic retina, microglia undergo early activation characterized by morphological changes, increased proliferation, and migration toward the inner retinal layers, even before the appearance of clinically detectable vascular lesions[21-22]. This early activation is accompanied by upregulation of proinflammatory signaling pathways, particularly nuclear factor kappa B (NF-κB), leading to increased production of cytokines such as interleukin (IL) -1β and tumor necrosis factor (TNF)-α[20,23].

Sustained microglial activation contributes directly to neuronal injury through multiple mechanisms. Proinflammatory cytokines released by activated microglia promote synaptic dysfunction, exacerbate oxidative stress, and induce apoptotic signaling in retinal neurons[22,24]. In addition, microglia-derived inflammatory mediators stimulate VEGF expression, thereby linking neuroinflammation to increased vascular permeability and BRB disruption[22,24]. With chronic activation, microglia progressively adopt a proinflammatory, scar-like phenotype characterized by persistent expression of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and complement components such as C1q and C3, together with sustained release of reactive oxygen and nitrogen species[25]. This microenvironment resembles a glial scar-like state, in which elevated levels of inhibitory extracellular matrix molecules, including chondroitin sulfate proteoglycans, and continuous cytokine signaling create a hostile milieu that restricts neuronal repair, synaptic plasticity, and axonal regeneration[26]. Moreover, evidence summarized in recent reviews suggests that microglial activation is not merely secondary to vascular leakage or ischemia, but instead represents an initiating event in diabetic retinal neurodegeneration[20,27]. Within this context, the formation of a proinflammatory glial scar-like environment may function as a sustained amplifier of neurodegeneration, maintaining chronic inflammatory signaling and preventing resolution of tissue injury even in the absence of overt ischemic damage[26]. This temporal relationship supports the view that microglia act as central amplifiers of neuroinflammatory signaling in the early stages of DRD.

Müller Cells Müller cells are the principal macroglia cells of the retina and play a critical role in maintaining neuronal homeostasis, regulating neurotransmitter recycling, and preserving BRB integrity[28]. In diabetes, Müller cells are highly sensitive to metabolic stress and undergo reactive gliosis, as evidenced by increased expression of glial fibrillary acidic protein (GFAP) and altered cellular morphology[29-30].

One of the most detrimental consequences of Müller cell dysfunction in DR is impaired glutamate clearance. Downregulation of glutamate transporters and disruption of glutamate–glutamine cycling lead to extracellular glutamate excitotoxicity, resulting in injury to retinal neurons, particularly retinal ganglion cells[29,31]. In parallel, dysfunctional Müller cells exhibit altered secretion of cytokines, growth factors, and vasoactive mediators, which further destabilize the NVU[20,28,32]. Although Müller cell activation may initially represent an adaptive response aimed at protecting neurons under metabolic stress, prolonged gliosis shifts this response toward a neurotoxic phenotype[30]. Chronic Müller cell dysfunction has been associated with BRB breakdown, enhanced inflammatory signaling, and increased susceptibility of retinal neurons to oxidative and ischemic injury[33]. Thus, Müller cells occupy a dual role in DRD, acting as early defenders of neural integrity but ultimately contributing to neurodegeneration when metabolic stress persists[27].

Astrocytes Astrocytes, though less abundant in the retina than Müller cells, play a crucial role in neurovascular coupling and metabolic support of inner retinal neurons[14]. In the diabetic retina, astrocytes exhibit phenotypic alterations characterized by abnormal polarization, reduced coverage of retinal vessels, and impaired metabolic coupling between neurons and the vasculature[34]. Astrocytic dysfunction compromises local oxygen and nutrient delivery to neurons, creating focal zones of metabolic insufficiency that exacerbate neuronal vulnerability. Disruption of astrocyte-mediated signaling also interferes with synaptic regulation and contributes to the failure of adaptive neurovascular responses under hyperglycemic conditions[35]. These changes have been linked to localized hypoxia and impaired synaptic transmission, further accelerating neurodegenerative processes[36].

Dysfunction of astrocytes reinforces the concept that diabetic retinal neurodegeneration arises from failure of coordinated glial support rather than isolated neuronal injury. Loss of effective astrocyte, neuron, and vascular interactions amplifies the deleterious effects of microglial inflammation and Müller cell gliosis, driving progressive NVU destabilization[12]. To facilitate an integrated understanding of cell-type specific neuroinflammatory mechanisms underlying diabetic retinal neurodegeneration, Table 1 summarizes the early cellular alterations, key molecular pathways, and downstream pathological consequences associated with microglia, Müller cells, and astrocytes in the diabetic retina[37]. Overall, rather

Table 1 Cell-type specific neuroinflammatory mechanisms contributing to retinal neurodegeneration in diabetic retinopathy

Cell type	Early alterations in diabetes	Key molecular pathways	Downstream pathological effects
Microglia	Early activation and migration toward inner retinal layers; morphological transformation; increased proliferation[21-22]	NF-κB activation; increased IL-1β, TNF-α; complement activation[20,23]	Synaptic dysfunction and neuronal apoptosis; amplification of neuroinflammation; induction of VEGF expression; promotion of vascular permeability and BRB disruption[12,22-24]
Müller cells	Reactive gliosis; upregulation of GFAP; impaired neurotransmitter recycling[29-30]	Reduced glutamate transport; altered cytokine and growth factor secretion[29,31]	Glutamate excitotoxicity; retinal ganglion cell injury; loss of neuroprotective support; destabilization of the BRB[28-33]
Astrocytes	Abnormal polarization; reduced vascular coverage; impaired metabolic coupling[34]	Disrupted astrocyte-neuron vascular signaling; altered metabolic support pathways[35-36]	Localized hypoxia; impaired synaptic regulation; failure of neurovascular coupling; increased neuronal vulnerability[34,36]
Integrated glial response	Sustained cross-talk among activated microglia and macroglia[12]	Chronic inflammatory signaling; oxidative and metabolic stress amplification[22]	Self-perpetuating neurodegenerative microenvironment; progressive NVU destabilization; facilitation of subsequent microvascular pathology[19-20]

NF-κB: Nuclear factor kappa B; IL-1β: Interleukin-1β; TNF-α: Tumor necrosis factor-α; VEGF: Vascular endothelial growth factor; BRB: Blood-retinal barrier; GFAP: Glial fibrillary acidic protein; NVU: Neurovascular unit.

than acting in isolation, microglia, Müller cells, and astrocytes engage in dynamic cross-talk that shapes the inflammatory and metabolic landscape of the diabetic retina. Persistent activation of these glial populations establishes a self-perpetuating cycle of neuroinflammation, excitotoxicity, and metabolic stress, ultimately leading to irreversible neuronal damage. This integrated glial response provides a connection between early neurodegeneration and subsequent microvascular pathology, reinforcing the central role of neuroinflammation in DRD.

KEY METABOLIC INSULTS DRIVING RETINAL NEURODEGENERATION IN DIABETIC RETINOPATHY

Chronic metabolic dysregulation is a defining feature of diabetes and represents a major upstream driver of retinal neurodegeneration. Rather than acting solely on the retinal vasculature, metabolic insults induced by hyperglycemia exert profound effects on neuronal viability, synaptic integrity, and glial homeostasis within the retinal NVU[1,28]. Accumulating evidence indicates that oxidative stress, advanced glycation end product (AGE) signaling, excitotoxic neurotransmitter imbalance, and mitochondrial dysfunction converge to create a neurotoxic microenvironment that accelerates retinal neurodegeneration in DR[12,37].

Oxidative Stress and Reactive Oxygen Species Overproduction Oxidative stress is one of the most extensively characterized metabolic insults in DR and plays a central role in retinal neurodegeneration[29,38]. Sustained hyperglycemia leads to excessive production of reactive oxidative species (ROS) through multiple pathways, including mitochondrial electron transport chain dysfunction, activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, and polyol pathway flux[38-39]. In the diabetic retina, elevated ROS levels overwhelm endogenous antioxidant defenses, resulting in lipid peroxidation, protein modification, and DNA damage[40].

Neuronal cells are particularly vulnerable to oxidative injury due to their high metabolic demand and limited regenerative capacity. Experimental and clinical evidence demonstrates that oxidative stress promotes retinal ganglion cell apoptosis and axonal degeneration, contributing directly to early functional deficits observed in diabetes[29,41]. Moreover, impaired activation of antioxidant transcriptional regulators, such as nuclear factor erythroid 2-related factor 2 (Nrf2), further exacerbates neuronal susceptibility to oxidative damage in diabetic retina[40]. In addition, oxidative stress does not act in isolation but amplifies neuroinflammatory signaling by activating redox-sensitive pathways in glial cells, thereby reinforcing the inflammatory milieu[41]. This bidirectional interaction establishes a vicious cycle that accelerates retinal neurodegeneration[39].

AGE-RAGE Signaling and Neurodegenerative Cascade Activation AGEs accumulate in retinal tissues as a consequence of chronic hyperglycemia and glycemic variability. Binding of AGEs to their receptor [Receptor for advanced glycation end products (RAGE)] activates multiple intracellular signaling cascades, including extracellular signal-regulated kinase (ERK1/2) and p38 mitogen-activated protein kinase (MAPK), which have been implicated in both inflammatory and neurodegenerative processes[42].

In the diabetic retina, AGE-RAGE signaling contributes to neuronal dysfunction by promoting oxidative stress, inflammatory cytokine release, and apoptotic signaling[43]. Reviews focusing on retinal neurodegeneration highlight that AGEs accumulate not only in vascular cells but also in neurons and glial cells, where they impair synaptic transmission and slow neural conduction[43]. This mechanism provides a molecular explanation for electrophysiological abnormalities detected by mfERG in early diabetes, even in the absence of overt vascular pathology. Furthermore, AGE-RAGE activation enhances glial reactivity, particularly in microglia and Müller

cells, thereby amplifying neuroinflammatory signaling within the NVU[42].

Glutamate Excitotoxicity and Impaired Neurotransmitter Homeostasis Maintenance of glutamate homeostasis is essential for retinal neuronal survival and synaptic function[44-45]. In DR, metabolic stress disrupts this balance through impaired glutamate uptake and recycling, primarily mediated by dysfunctional Müller cells[46]. Reduced expression and activity of glutamate transporters, including glutamate–aspartate transporter (GLAST) and excitatory amino acid transporters (EAATs), result in extracellular glutamate excitotoxicity[47].

Excess extracellular glutamate triggers excitotoxic signaling through overactivation of ionotropic glutamate receptors, leading to calcium influx, mitochondrial overload, and activation of apoptotic pathways in retinal neurons[45]. Retinal ganglion cells are particularly susceptible to excitotoxic injury, which contributes to early neuronal loss and thinning of inner retinal layers detected by OCT[45]. This mechanism provides a direct metabolic explanation for structural neurodegenerative changes observed in diabetic patients without advanced microvascular disease. Moreover, glutamate excitotoxicity interacts synergistically with oxidative stress and neuroinflammation, further lowering the threshold for neuronal injury in the diabetic retina[48].

Mitochondrial Dysfunction and Irreversible Neuronal Injury Mitochondrial dysfunction represents a final common pathway through which diverse metabolic insults converge to induce retinal neurodegeneration[49-50]. Hyperglycemia-induced oxidative stress, AGE-RAGE signaling, and excitotoxic calcium influx collectively impair mitochondrial integrity and bioenergetic capacity in retinal neurons[49]. Studies summarized in recent comprehensive reviews indicate that mitochondrial damage in diabetic retinas is characterized by loss of membrane potential, impaired adenosine triphosphate (ATP) production, and release of proapoptotic factors such as cytochrome c, ultimately leading to neuronal apoptosis[49-50]. Notably, mitochondrial dysfunction may persist even after glycemic control is improved[51]. Once established, mitochondrial dysfunction contributes to irreversible neuronal injury and limits the capacity for functional recovery[52-53].

Taken together, oxidative stress, AGE-RAGE signaling, excitotoxic neurotransmitter imbalance, and mitochondrial dysfunction form an interconnected network of metabolic insults that preferentially target retinal neurons and glial cells. Rather than acting primarily through vascular injury, these metabolic pathways converge on neuronal vulnerability and NVU destabilization, thereby driving early retinal neurodegeneration and predisposing the retina to subsequent microvascular pathology[42,51].

NEUROPROTECTIVE STRATEGIES AND EMERGING THERAPEUTIC TARGETS IN DIABETIC RETINAL DISEASE

Recognition of retinal neurodegeneration as a central pathological component of DR has important therapeutic implications. Current clinical interventions, including laser photocoagulation and anti-VEGF therapy, primarily target late-stage vascular abnormalities and have limited efficacy in preventing early neuronal dysfunction or restoring visual function once neurodegeneration is established[54-55]. These limitations underscore the need for treatment strategies that directly address neural and glial pathology within the retinal NVU[42]. However, translation of neuroprotective strategies into clinical practice faces substantial hurdles, including challenges related to drug delivery, BRB penetration, and the lack of validated neural endpoints in clinical trials. Additionally, a critical gap remains between the robust efficacy seen in animal models and the variable outcomes in clinical trials.

Targeting Oxidative Stress and Neuroinflammation Given the central role of oxidative stress and neuroinflammation in driving retinal neurodegeneration, antioxidant and anti-inflammatory approaches have emerged as logical neuroprotective strategies[48,56]. Experimental studies and comprehensive reviews indicate that reducing ROS levels can attenuate neuronal apoptosis, preserve synaptic function, and stabilize mitochondrial integrity in the diabetic retina[49].

Modulation of inflammatory signaling pathways, particularly those involving microglial activation and NF-κB-dependent cytokine production, has also shown promise in experimental models[57-59]. Preclinical studies demonstrate that suppression of proinflammatory mediators such as IL-1β and TNF-α reduces neuronal injury and limits secondary vascular permeability changes[48].

However, the translation of these findings to human clinical practice remains limited. Unlike standardized animal models, human efficacy is confounded by disease heterogeneity and the challenge of delivering therapeutic concentrations across the BRB. Systemic administration is often limited by the blood-retinal barrier, which restricts the penetration of many neuroprotective compounds. In contrast, intravitreal delivery can achieve effective retinal exposure but raises concerns regarding invasiveness, dosing frequency, and long-term safety, particularly in the context of chronic neuroprotective treatment[54,60-61]. Thus, optimization of delivery routes remains a major barrier to the clinical implementation of antioxidant and anti-inflammatory neuroprotective therapies[60-61].

Neurotrophic Factors and Restoration of Neuronal Support Impaired neurotrophic support is a key feature of diabetic retinal neurodegeneration. Reduced availability of neurotrophic factors such as nerve growth factor (NGF)

and brain-derived neurotrophic factor (BDNF) has been consistently reported in diabetic retinas and is associated with increased neuronal vulnerability[62]. Therefore, restoration of neurotrophic signaling has been proposed as a neuroprotective strategy. Reviews focusing on NGF and related pathways indicate that exogenous supplementation or enhancement of endogenous neurotrophic factor signaling can promote neuronal survival, support synaptic integrity, and contribute to repair of the NVU[63]. In the realm of clinical validation, the distinction between preclinical promise and clinical reality is evident. While neurotrophic factors show strong efficacy in animal models, human trials face delivery hurdles, including poor retinal bioavailability following systemic administration and the need for repeated intravitreal injections[54,60-61].

Topical administration of neuroprotective agents, such as brimonidine, has been evaluated in DR within the EUROCONDOR clinical trial framework, providing important proof of concept evidence that neuroprotection can be safely explored in early-stage disease, although therapeutic efficacy remains modest[64-65]. In parallel, sustained-release intravitreal delivery platforms originally developed for retinal neurodegenerative disorders, such as the brimonidine drug delivery system (Brimo DDS) evaluated in geographic atrophy, have demonstrated the translational feasibility of long-acting intravitreal neuroprotective strategies. At present, the clinical evidence is mainly limited to early trials. More reliable data from Phase III clinical trials are needed to confirm its effectiveness in preventing the progression of DR.

In addition to direct effects on neurons, neurotrophic factors exert modulatory actions on Müller cells and microglia, helping to shift glial responses from a proinflammatory to a neuroprotective phenotype[63]. Although clinical translation remains limited, neurotrophic factor-based therapies remain a promising research direction as a strategy for vascular-targeted treatment of DR[63].

Modulation of Glial Cell Function as a Therapeutic Target Given the pivotal role of glial cells in coordinating neuroinflammatory and metabolic responses, targeting glial dysfunction represents a promising therapeutic avenue.

Extensive preclinical evidence demonstrates that suppressing aberrant microglial activation or reinstating Müller glia-mediated homeostatic support effectively mitigates glutamate excitotoxicity, attenuates pro-inflammatory cascades, and safeguards neuronal integrity in experimental models of diabetes[58]. In particular, interventions that improve glutamate clearance by Müller cells or prevent chronic reactive gliosis may protect retinal neurons from excitotoxic injury and secondary degeneration[46].

However, unlike in animal models, selective modulation of glial phenotypes in the human retina is complicated by the dual role of glial cells in both neuroprotection and inflammation. Furthermore, no glial-specific therapeutic agents have yet reached Phase III clinical trials for DRD, largely due to the challenge of delivering drugs specifically to glial populations without disrupting their homeostatic functions, and off-target effects may limit clinical applicability[66]. These considerations further emphasize the need for therapies that fine-tune, rather than broadly suppress, glial responses within the NVU. Therefore, while the biological rationale is strong, clinical implementation requires the development of more precise, cell-targeted delivery systems to bridge this gap.

Ischemia-Reperfusion Injury and Mitochondrial Protection Ischemia-reperfusion injury and mitochondrial dysfunction represent critical downstream events that exacerbate retinal neurodegeneration in diabetes[49-50]. In preclinical models, agents that stabilize mitochondrial membrane potential or scavenge mitochondrial ROS have shown robust neuroprotective effects[51-52]. Evidence summarized that preserving mitochondrial function can mitigate neuronal apoptosis, reducing cytochrome c release, enhancing cellular antioxidant capacity and limit irreversible functional loss[49,52]. Additionally, mitochondrial protection may also counteract the phenomenon of metabolic memory, in which prior hyperglycemic exposure leads to persistent neuronal damage despite subsequent glycemic control[51-52]. However, few specific mitochondrial stabilizers have successfully translated into approved therapies from a clinical perspective.

From a translational perspective, systemic agents with pleiotropic metabolic and neuroprotective effects may offer advantages. Fenofibrate, which has demonstrated efficacy in large Phase III clinical trials (FIELD, ACCORD-Eye, and LENS) in reducing DR progression, is increasingly recognized to exert benefits that extend beyond lipid lowering, potentially involving anti-inflammatory, antioxidative, and neuroprotective mechanisms within the retina[54,67-68]. Unlike purely experimental drugs, fenofibrate provides a successful example of clinical transformation. Thus, fenofibrate represents a model for repurposing systemic drugs with neuroprotective potential to bridge the gap between experimental neuroprotection and clinical vascular outcomes.

Figure 2 illustrates a framework in which neuroprotective interventions, including modulation of oxidative stress, neuroinflammation, glial dysfunction, mitochondrial impairment, and reduced neurotrophic support, converge to stabilize retinal NVU function and complement conventional vascular-targeted therapies[50].

All in all, these observations support a paradigm shift from treating DR solely as a vascular complication toward managing it as a neurovascular degenerative disease. Rather than

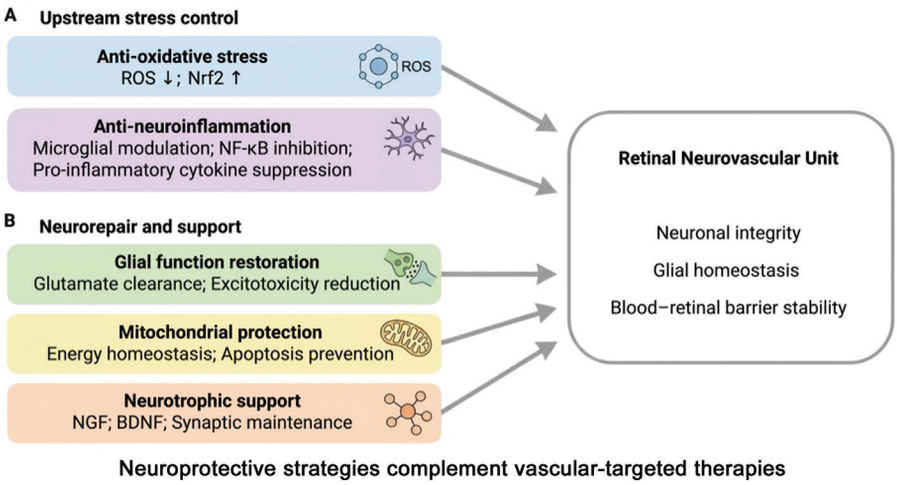

Figure 2 Neuroprotective strategies targeting retinal neurovascular unit dysfunction in diabetic retinal disease This schematic summarizes emerging neuroprotective approaches aimed at preserving retinal neuronal integrity and restoring NVU homeostasis in DRD. Therapeutic strategies are grouped into upstream stress control (A), including anti-oxidative stress (reducing ROS) level and increasing Nrf2 level and anti-neuroinflammatory interventions (microglial modulation, NF-kB inhibition and pro-inflammatory cytokine suppression), which mitigate early metabolic and inflammatory insults; Neurorepair and support (B), encompassing restoration of glial function (glutamate clearance, excitotoxicity reduction), mitochondrial protection (energy homeostasis, apoptosis prevention), and enhancement of neurotrophic support (regulating NGF and BDNF, synaptic maintenance), thereby promoting neuronal survival, synaptic maintenance, and long-term NVU stability. ROS: Reactive oxidative species; Nrf2: Nuclear factor erythroid 2–related factor 2; NF-κB: Nuclear factor kappa B; NGF: Nerve growth factor; BDNF: Brain-derived neurotrophic factor; DRD: Diabetic retinal disease; NVU: Neurovascular unit.

replacing existing vascular-focused therapies, neuroprotective approaches are more likely to complement them, particularly when applied at early stages of disease before irreversible neuronal loss occurs. Successful clinical translation will require improved drug delivery strategies, early diagnostic biomarkers of neurodegeneration, and clinical trial designs that incorporate functional and neuroprotective endpoints alongside vascular outcomes.

CONCLUSIONS AND FUTURE PERSPECTIVES

Accumulating evidence clearly demonstrates that retinal neurodegeneration is not a secondary epiphenomenon of DR but rather a fundamental and early pathological process that shapes disease initiation and progression. Functional abnormalities detected by electrophysiological testing, structural neuronal loss revealed by optical coherence tomography, and widespread glial dysfunction collectively indicate that neural injury precedes and contributes to subsequent microvascular damage in the diabetic retina. These observations challenge the traditional microangiopathy-centered paradigm and support a reconceptualization of DR as a neurovascular degenerative disorder[69]. Within this framework, the concept of DRD provides a more comprehensive description of the integrated neural, glial, and vascular pathology induced by chronic metabolic stress. Disruption of the retinal NVU, driven by neuroinflammation, oxidative stress, excitotoxicity, and mitochondrial dysfunction, emerges as a unifying mechanism linking early neuronal impairment to later vascular complications. These processes preferentially target retinal neurons and glial cells, offering a mechanistic explanation for visual dysfunction that cannot be fully accounted for by vascular lesions alone.

From a clinical perspective, recognition of retinal neurodegeneration as a core pathological axis has significant implications for diagnosis and treatment. Current therapeutic strategies predominantly address advanced microvascular abnormalities and often fail to prevent progressive visual decline, particularly in patients with DME or early functional impairment. This mismatch between vascular lesion control and persistent visual dysfunction underscores the need for diagnostic frameworks that capture early neural injury. Incorporating neural biomarkers into clinical assessment may enable earlier detection of disease activity and provide more sensitive endpoints for therapeutic intervention[46]. In the near term, advances in high-resolution optical coherence tomography, OCT angiography, and artificial intelligence-based image analysis offer feasible tools for extracting neural and glial signatures, such as RNFL thinning patterns, ganglion cell complex alterations, and subtle functional structural dissociations. In parallel, emerging liquid biopsy approaches, including circulating inflammatory mediators, neurofilament-related proteins, and metabolic stress markers, warrant systematic evaluation as minimally invasive indicators of retinal neurodegeneration, particularly in individuals with prediabetes or early-stage diabetes.

Therefore, future therapeutic development should therefore move beyond a purely vascular focus and embrace neuroprotective and NVU-stabilizing strategies. Approaches targeting oxidative stress, neuroinflammation, glial dysfunction, impaired neurotrophic support, and mitochondrial injury have shown promising experimental and preclinical evidence of efficacy in preserving retinal neuronal integrity. In the short to medium term, priority should be given to repurposing characterized neuroprotective agents and integrating them with existing anti-VEGF or laser-based therapies within stage-adapted, multimodal treatment paradigms. Rather than replacing anti-VEGF or laser-based therapies, such strategies are likely to be most effective when integrated into a multimodal treatment paradigm tailored to disease stage and individual risk profiles. In the longer term, precision medicine approaches that combine longitudinal imaging, functional testing, and molecular profiling may enable personalized neurovascular protection strategies across the diabetic spectrum.

Several challenges remain before neuroprotective strategies can be fully translated into clinical practice. These include the identification of robust and reproducible neural biomarkers, clarification of optimal therapeutic windows, and the design of clinical trials that incorporate functional and neurodegenerative endpoints alongside vascular outcomes. Addressing these challenges will require close integration of basic mechanistic studies, advanced imaging technologies, computational analytics, and carefully designed early-phase clinical trials focused on neural preservation rather than late-stage vascular rescue alone.

Overall, in this review, we systematically summarize and integrate current evidence demonstrating that retinal neurodegeneration constitutes a core and early pathological axis in DRD. Moreover, this review provides a unified perspective that bridges basic pathophysiology with translational and clinical implications by focusing on cell type-specific neuroinflammatory responses, key metabolic insults, and emerging neuroprotective strategies. By reviewing a staged translational roadmap from mechanistic discovery to biomarker development and clinical intervention, this review aims to inform the development of earlier diagnostic strategies and targeted therapies addressing retinal neurodegeneration and NVU dysfunction.

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